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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/994,468	12/19/1997	STEWART D. LYMAN	2813-L	6662

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	30

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/994468	Applicant(s) LYMAN
	Examiner GAMBEL	Art Unit 644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 9/9/02; 3/4/03

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1-8, 17-26, 29-36

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1-8, 17-26, 29-36

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☑ objected to by the Examiner. SEE OFFICE ACTION

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. The request filed 3/4/03 (Paper No. 27) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/994,468 is acceptable and a CPA has been established An Office Action on the CPA follows.

Applicant's amendment, filed 9/9/02 (Paper No. 24), has been entered.
Claims 9-16 and 27-28 have been canceled.
Claims 1-7, 19-25 and 29-30 have been amended.

Applicant's amendment, filed 3/4/03 (Paper No. 27), has been entered.
Claims 17-26 have been amended.
Claims 31-36 have been added.

Claims 1-8, 17-26 and 29-36 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 3/4/03 (Paper No. 27)
The rejections of record can be found in the previous Office Action (Paper Nos. 14/21/25).

3. Applicant's amendment, filed 3/4/03 (Paper No. 27), notes that the priority date of the instant claims enjoy the benefit of USSN 08/209,502, filed 3/7/94.

4. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the form PTO-948 previously sent in Paper No. 21..

INFORMATION ON HOW TO EFFECT DRAWING CHANGES
A. Correction of Informalities -- 37 CFR 1.85
New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

5. Upon reconsideration, the previous rejection under 35 U.S.C. 112, first paragraph, (written description), with respect to the instant claims have been withdrawn.

6. Claims 1-8, 17-26 and 29-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hemopoietic cell expansion media comprising human or mouse flt3 ligand or comprising a soluble polypeptide consisting of amino acids 28-160 of SEQ ID NO: 6 does not provide enablement for hematopoietic cell expansion media comprising

"(b) polypeptides comprising a fragment of amino acids 28-160 of SEQ ID NO: 6, wherein the fragment binds flt3",

"(c) polypeptides comprising a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO: 6 and

(d) polypeptides comprising a fragment of a polypeptide that is at least 90% identical to amino acids 28-160, wherein the fragment binds flt3".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 3/4/03 (Paper No. 27), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

Again, applicant argues in conjunction with various legal decisions that a patent need not teach and preferably omits what is well known in the art and the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

Applicant submits that the skilled artisan would not have to undertake undue experimentation to make and use the claimed invention because determining flt3 ligand polypeptides that are at least 90% identical to SEQ ID NO: 6 is considered routine in the art and therefore would not constitute undue experimentation.

Applicant submits the reduction to practice of two working examples of mouse and human flt3 ligand as well as direction and guidance as to how to make flt3 ligands variants that bind flt3 receptor in conjunction with known screening formats would have resulted in routine experimentation at the time the invention was made.

Again, applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any "flt3 ligand polypeptide" of any "mammal" or "at least 90% identical to the amino acids 28-160 of SEQ ID NO: 6" as well as 'fragments thereof"; yet the instant specification does not provide sufficient guidance and direction as to the structural features of said scope of "flt3 ligand polypeptides" and "fragments thereof" and the correlation between the chemical structure and the desired molecules or specificities. The reliance on the disclosed limited examples set forth in the specification does not support the enablement for any "flt3 ligand polypeptide" or "fragment thereof", encompassed by the claimed invention.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "flt3 ligand polypeptides" and "fragments"with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "mammalian flt3 ligands" encompassed by the claimed invention.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the mouse and human flt3 ligand disclosed in the specification as filed does not appear to provide sufficient enabling support for any mammalian flt3 ligand polypeptide and fragment thereof encompassed by the claimed invention and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2).

A person of skill in the art is not enabled to make and use the "flt 3 ligand polypeptides" and "fragments thereof", as recited in the claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for the ability to bind flt3 for the expansion of hemopoietic cells. A person of skill in the art could not predict which particular amino acid sequences of "flt 3 ligand polypeptides" and "fragments thereof" are essential and could be used in a hemopoietic cell expansion methods. It is not clear that the skilled artisan could predict the efficacy of the breadth to the "flt3 ligand polypeptides and "fragments thereof", encompassed by the claims, including "variants which may comprise conservatively substituted sequences" *page 8, lines 25-27 of the instant specification).

Without sufficient guidance, making and using "flt3 ligand polypeptide", including those that are "at least 90% identical to SEQ ID NO: 6" and "fragments thereof" would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant's arguments are not found persuasive.

7. Claims 1-8, 17-26 and 29-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9 and 10 of copending USSN 08/399,404 for the reasons of record..

Again, applicant's previous request for this rejection to be held in abeyance has been acknowledged.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
May 30, 2003